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Multicenter phase II trial of preoperative induction chemotherapy followed by chemoradiation with docetaxel and cisplatin for locally advanced esophageal carcinoma (SAKK 75/02)

T. Ruhstaller[1]*, L. Widmer[2], J. C. Schuller[3], A. Roth[4], V. Hess[5], W. Mingrone[6], R. von Moos[7], M. Borner[8], B. C. Pestalozzi[9], S. BalmerMajno[10], D. Köberle[1], L. Terraciano[11], A. Schnider[12], S. Bodis[13] & R. Popescu[14] for the Swiss Group for Clinical Cancer Research (SAKK)

[1]*Department of Oncology and Hematology, Kantonsspital, St Gallen, St Gallen;* [2]*Department of Oncology, Triemlispital Zurich, Zurich;* [3]*Coordination Center, SAKK Bern, Bern;* [4]*Oncosurgery, Department of Surgery, University Hospital of Geneva, Geneva;* [5]*Division of Medical Oncology, Department of Internal Medicine, University Hospital of Basel, Basel;* [6]*Department of Oncology and Hematology, Kantonsspital Aarau, Aarau;* [7]*Department of Medical Oncology and Hematology, Kantonsspital Graubünden, Chur;* [8]*Institute of Medical Oncology, Inselspital Bern, Bern;* [9]*Department of Oncology, University Hospital of Zurich, Zurich;* [10]*Department of Radiation Oncology, University Hospital of Geneva, Geneva;* [11]*Institute of Pathology, University Hospital of Basel, Basel;* [12]*Department of Surgery, Triemlispital Zurich, Zurich;* [13]*Institute for Radio-Oncology, Kantonsspital Aarau, Aarau and* [14]*Tumor Center, Hirslanden Clinic Aarau, Aarau, Switzerland*

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Background: This multicenter phase II study investigated the efficacy and feasibility of preoperative induction chemotherapy followed by chemoradiation and surgery in patients with esophageal carcinoma.

Patients and methods: Patients with locally advanced resectable squamous cell carcinoma or adenocarcinoma of the esophagus received induction chemotherapy with cisplatin 75 mg/m^2 and docetaxel (Taxotere) 75 mg/m^2 on days 1 and 22, followed by radiotherapy of 45 Gy (25 × 1.8 Gy) and concurrent chemotherapy comprising cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 weekly for 5 weeks, followed by surgery.

Results: Sixty-six patients were enrolled at eleven centers and 57 underwent surgery. R0 resection was achieved in 52 patients. Fifteen patients showed complete, 16 patients nearly complete and 26 patients poor pathological remission. Median overall survival was 36.5 months and median event-free survival was 22.8 months. Squamous cell carcinoma and good pathologically documented response were associated with longer survival. Eighty-two percent of all included patients completed neoadjuvant therapy and survived for 30 days after surgery. Dysphagia and mucositis grade 3/4 were infrequent (<9%) during chemoradiation. Five patients (9%) died due to surgical complications.

Conclusions: This neoadjuvant, taxane-containing regimen was efficacious and feasible in patients with locally advanced esophageal cancer in a multicenter, community-based setting and represents a suitable backbone for further investigation.

Key words: chemoradiation, esophageal carcinoma, esophagus, induction chemotherapy, preoperative

introduction

Most patients with newly diagnosed carcinoma of the esophagus present with locally advanced disease. Because of high rates of locoregional and distant failure, there has been much interest in combining local and systemic therapy. Research conducted to date shows that adjuvant therapy does not improve outcomes [1–4]. Thus, current research is focusing on neoadjuvant strategies. In clinical practice, preoperative chemoradiation is commonly used, although this strategy has not shown a survival benefit over surgery alone in adequately powered phase III trials [5–12], only in some meta-analyses [13, 14]. The additional impact of surgery following chemoradiation also remains unclear. Two randomized trials showed an improvement in locoregional control following surgery, but without any benefit in survival [15, 16].

The accepted standard approaches for locally advanced esophageal cancer therefore include neoadjuvant chemotherapy with or without radiation therapy and definitive chemoradiation. Other variables which can influence treatment outcome include different histologies implying different clinical biology, the exact location of the tumor in the esophagus which influences morbidity of surgery and several different techniques of surgery and radiation therapy. Together with the relative rarity of this disease and the necessity for intensive

Correspondence to: Dr T. Ruhstaller, Fachbereich Onkologie/Hämatologie, Kantonsspital St Gallen, 9007 St Gallen, Switzerland. Tel: +41-71-494-11-77; Fax: +41-71-494-63-68; E-mail: thomas.ruhstaller@kssg.ch

multidisciplinary teamwork in diagnostics and therapeutics, large multicenter studies are difficult to carry out. Thus, many pivotal phase III trials were carried out in single high-volume institutions [5–7, 9, 10] and were often underpowered. However, the results from studies carried out in highly specialized centers often cannot be easily translated into clinical practice.

Based on these considerations, we initiated a nationwide, multicenter phase II study in Switzerland investigating neoadjuvant chemoradiation. In Switzerland, there are no high-volume centers according to the international standards; however, the essential preoperative multidisciplinary evaluations are well established in both academic and nonacademic centers. The neoadjuvant regimen under investigation started with two cycles of induction chemotherapy in order to prolong systemic treatment and to reduce the severity of dysphagia before starting chemoradiation. Fluorouracil, commonly used in other studies in combination with cisplatin, was replaced by a taxane to reduce mucositis during chemoradiation. Chemotherapy was administered weekly during radiation therapy in an attempt to enhance synergy with radiotherapy.

patients and methods

This was an open-label, multicenter phase II study. The protocol was approved by the ethics committee of each participating institution, and all patients gave written informed consent.

patient selection and evaluation

Previously untreated patients with locally advanced, histologically confirmed squamous cell carcinoma or adenocarcinoma of the thoracic esophagus including the gastroesophageal junction (Siewert type I), aged 18–70 years, with a World Health Organization performance status of zero or one, adequate hematologic, renal and hepatic function were eligible. The tumor had to be locally advanced but resectable (stage T_3/N_0, T_{1-3}/N_+ or T_4/N_x, if technically resectable with curative intent). Before registration, a multidisciplinary team evaluated each patient to determine potential resectability and operability. Patients were not eligible if metastases were present including cervical or celiac lymph node involvement (M1a), if they had concurrent cancer or uncontrolled significant comorbidity.

Pretreatment staging consisted of complete medical history, physical examination, upper endoscopy with biopsy, helical computed tomography (CT) scans of the chest and abdomen, endoscopic ultrasound (EUS) and bronchoscopy if airway infiltration was suspected. A laparoscopy for tumors of the lower third of the esophagus was optional. Positron emission tomography (PET) or PET–CT staging was strongly recommended but not mandatory. Obstructive tumors were considered locally advanced and eligible for the trial even if a complete EUS was not feasible. Lymph nodes were usually classified according to the EUS visual lymph node assessment criteria of malignancy [17]. Any mismatch of different staging methods was discussed by a multidisciplinary team including further investigations and whether the patient would be eligible for the trial.

treatment plan

Preoperative treatment consisted of two cycles of induction chemotherapy followed by chemoradiation. Induction chemotherapy consisted of cisplatin 75 mg/m^2 and docetaxel (Taxotere, Aventis Pharma AG, Switzerland) 75 mg/m^2 administered i.v. on days 1 and 22. Chemoradiation started after the second induction chemotherapy cycle. Three-dimensional (3D) conformal radiotherapy of 45 Gy (25 fractions of 1.8 Gy) was given over 5 weeks with 6–18 MV photons. The planning target volume included all known areas of disease with a 5-cm cranial and caudal margin and a 2-cm lateral margin. Spinal cord dose was limited to 36 Gy. All patients had 3D planning, the correction of lung inhomogeneity was optional. Concomitant chemotherapy consisted of i.v. cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 administered weekly for 5 weeks on an outpatient basis.

Surgery was scheduled 3–8 weeks after the completion of chemoradiation. To proceed to surgery, patients were required to have no evidence of newly detected stage M1 and/or inoperable T4 disease after repeated chest and abdominal CT scanning and EUS. En bloc R0 resection according to the International Union Against Cancer had to be carried out. By definition, radical resection refers to the primary and to lymphatic drainage areas as well. According to the localization of the tumor and the preference of the surgeon, a thoraco-abdomino-cervical, thoraco-abdomino-thoracal or abdomino-thoracal approach was taken. A complete two-field lymphadenectomy was mandatory including resection of the azygos vein. For adenocarcinoma of the gastroesophageal junction (Siewert type I), a transhiatal partial esophagogastrectomy was allowed including abdominal and partial para-esophageal lymphadenectomy. Barrett's mucosa and epithelial dysplastic mucosa had to be resected with the tumor. Reconstruction could be done either with a stomach conduit or with a transverse or ileocolon conduit according to the center's preference.

dose modifications and follow-up

Toxicity was evaluated by National Cancer Institute—Common Toxicity Criteria version 2.0. For the second induction chemotherapy cycle, cisplatin and docetaxel were both postponed if the absolute neutrophil count (ANC) was <1500/μl or if the platelet count was <100 000/μl. To start chemoradiation, an ANC of ≥1000/μl and platelet counts of ≥75 000/μl were necessary. During chemoradiation, docetaxel was omitted for 1 week if the ANC was <1000/μl or platelet counts were <50 000/μl. Radiotherapy and both drugs were stopped for 1 week if ANC was <500/μl and/or platelet counts <25 000/μl after weekly reassessment. In case of febrile neutropenia during chemoradiation, docetaxel was omitted whereas radiotherapy and cisplatin were continued as judged by the local investigator.

In case of tumor- or treatment-induced dysphagia, tube feeding was optional. Early insertion of a feeding tube was, however, recommended. In cases of grade 3 therapy-induced esophagitis, radiotherapy was continued, but the decision to continue chemotherapy depended upon the local investigator. In cases of grade 4 esophagitis, both chemotherapy and radiation were interrupted until toxicity resolved to grade 3.

Cisplatin was replaced by carboplatin if grade 3 peripheral neuropathy, grade 2 hearing impairment or creatinine clearance <50 ml/min occurred. For the second cycle of induction chemotherapy, carboplatin was given at a dose of area under the concentration–time curve (AUC) 6 mg·min/ml, and carboplatin AUC 2 mg·min/ml was given throughout chemoradiation. In case of R1/2 resection, it was up to the local investigator to define possible further local therapy.

Follow-up included CT scans and was carried out three monthly following surgery or treatment failure during the first year, six monthly during the next 3 years and yearly thereafter unless otherwise indicated clinically. Endoscopic examination was carried out only if there were new symptoms suggestive of local failure.

criteria for response and survival

Histopathological response was based on pathology findings after esophagectomy. The specimens were evaluated according to the standardized procedures by the local pathologists. The histopathological response was classified according to the Mandard classification of 'tumor regression grade' (TRG) [18]. TRG1 is defined as complete regression, absence of histologically identifiable residual cancer and fibrosis extending

through the different layers of the esophageal wall; TRG2 as presence of rare residual cancer cells scattered through the fibrosis and TRG >2 as increased number of residual cancer cells. All specimens were centrally reviewed at the University of Basel by an experienced pathologist; in three cases, the TRG by the local pathologist had to be revised.

Feasibility rate was defined as the proportion of patients who completed the whole neoadjuvant therapeutic regimen and who survived for 30 days after surgery. Event-free survival was defined as time from registration to disease progression, relapse or death, whichever occurred first. The pattern of failure was determined by the localization of tumor at the time of relapse. Any relapse within the previous radiotherapy field was considered a 'local failure'.

statistics

We evaluated two primary end points, pathological complete remission rate (pCR) and feasibility rate. The sample size was calculated to have a power of 90% and a significance level of 5% based on Bryant and Day's design [19], which is a modification of Simon's two-stage design for two primary end points [20].

A pCR rate (i.e. TRG1) of 30% was considered promising for further study, and a rate of 15% was considered insufficient. A feasibility rate of 70% was considered acceptable while a rate of 50% was considered unacceptable.

The trial was to be stopped after a first stage of 22 patients if only three patients or fewer had a TRG of 1 or if only 11 patients had successfully completed treatment. Otherwise, the trial plan was to accrue 44 more patients in a second stage. Hence, the sample size for this study was 66.

Survival analysis was done on an intention-to-treat basis.

Serious adverse events and response rates were continuously monitored by the Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) Coordinating Center. The interim results were presented to the SAKK Executive Committee before a definitive decision about continuation or early stopping was made.

results

patient and tumor characteristics

From July 2003 to June 2006, 66 patients were enrolled at 11 centers. Seven of the centers were non-university hospitals and contributed 70% of the patients. Patient and tumor characteristics are listed in Table 1. Most patients were male and had stage T3, N0–1 disease. Four patients did not undergo endosonography because of obstructing esophageal lesions; their stage was therefore at least T3 by definition. A PET scan or an integrated PET–CT scan was carried out at baseline in 56 patients; 8 of the 10 remaining patients were treated at centers where PET was not yet available, one patient refused the PET scan and one PET scan was carried out after starting therapy.

treatment outcomes

An accrual and treatment summary is depicted in Figure 1. Four patients progressed during neoadjuvant therapy; three of whom had newly diagnosed distant disease.

Four patients did not undergo surgery, one due to severe lung embolism and in three cases because the tumor was not expected to be R0 resectable even though the tumor had not progressed under neoadjuvant therapy. In addition, one patient was operated after 3-month delay after reversing his initial decision to refuse surgery. Eighty-two percent of all patients fulfilled in an intention-to-treat analysis the primary endpoint for feasibility according to the definition in the protocol (completing neoadjuvant therapy and surviving for 30 days after surgery).

Table 1. Patient and Tumor Characteristics

	Adenocarcinoma		Squamous cell carcinoma		Total	
	n	%	*n*	%	*n*	%
No. of patients	36	100	30	100	66	100
Age, years						
Median	61		59		61	
Range	35–70		41–70		35–70	
Sex						
Male	31	86	25	83	56	85
Female	5	14	5	17	10	15
Clinical stage						
T_1N_1	1	3	0	0	1	2
T_2N_1	6	17	5	17	11	17
T_3N_0	5	14	4	13	9	14
T_3N_1	22	61	18	60	40	61
T_3N_x	2	6	2	7	4	6
T_4N_1	0	0	1	3	1	2
WHO grade						
1	2	6	3	10	5	8
2	16	44	17	57	33	50
3	16	44	10	33	26	39
Not determined	2	6	0	0	2	3
Barrrett's metaplasia	12	33	1	3	13	20
ECOG performance status						
0	24	67	21	70	45	68
1	12	33	9	30	21	32
Dysphagia grade[a]						
0/1	27	75	18	60	45	68
2	8	22	11	37	19	29
3	0	0	1	3	1	2
4	1	3	0	0	1	2

[a]According to National Cancer Institute—Common Toxicity Criteria version 2.0.
WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group.

The surgical outcome is listed in Table 2. Three patients with squamous cell carcinoma in the distal part of the esophagus received a transhiatal resection only, which formally was a protocol violation. According to the protocol, surgical mortality was defined as death occurring within 30 days postoperatively and affected only one patient (1.8%). However, another four patients died after 30 days postoperatively due to surgical complications (Table 2).

Among the 57 patients who underwent surgery, 53 (93%) had disease-free margins. In an intention-to-treat analysis, the second primary end point pCR (TRG1) was reached by 23% of all included patients, an additional 24% showed a near complete remission (TRG2). It is worth to mention that 38% of all patients with squamous cell cancer achieved pCR compared with only 16% with adenocarcinoma.

At a median follow-up of 29 months (range 5–53 months), 39 patients were still alive. The Kaplan–Meier estimates of overall survival rate at 2 and 3 years was 66% and 53%, respectively. The median overall survival and median event-free

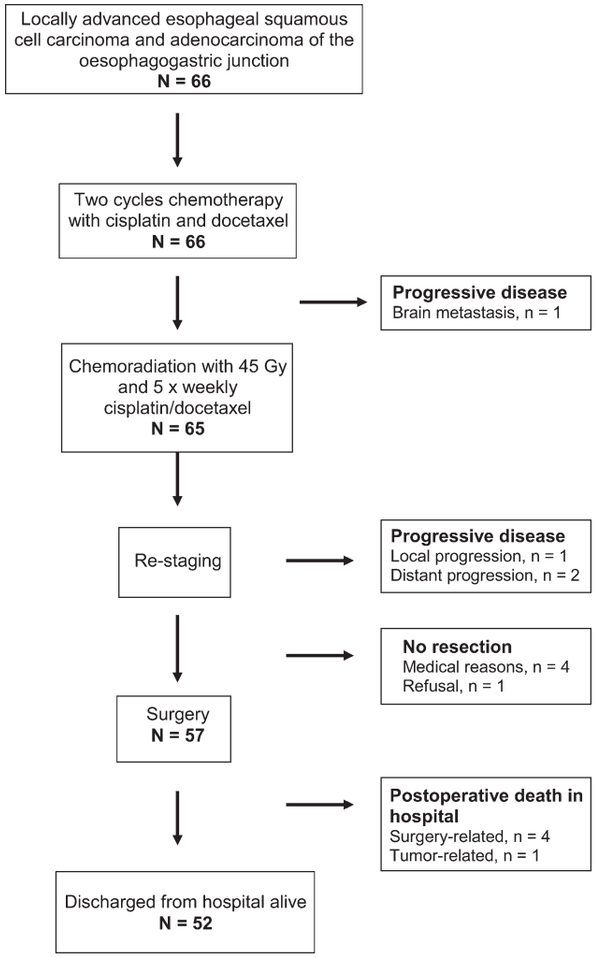

Figure 1. Accrual and treatment summary.

Table 2. Surgical outcomes: histopathological response, morbidity and mortality

	Adenocarcinoma		Squamous cell carcinoma		Total	
	n		*n*		*n*	
Eligible patients	36		30		66	
No surgery performed	5		4		9	
	n	%	*n*	%	*n*	%
Total surgery	31	100	26	100	57	100
Type of surgery						
Abdomino-thoracal resection	13	42	23	88	36	63
Transhiatal resection	18	58	3	12	21	37
Resections achieved						
R0	29	94	24	92	53	93
R1	1	3	2	8	3	5
R2	1	3	0	0	1	2
Histopathological response rate						
TRG 1 (pCR)	5	16	10	38	15	26
TRG 2	8	26	8	31	16	28
TRG 3–5	18	58	8	31	26	46
Deaths due to						
Complications of surgery	1	3	4	15	5	9
ARDS and multiorgan failure	0	0	3	12	3	5
Anastomotic leakage and fatal bleeding	0	0	1	4	1	2
Anastomotic leakage/sepsis	1	3	0	0	1	2
Nonfatal complications						
Pneumonia	3	10	5	19	8	14
Other infection	5	16	2	8	7	12
Intra-abdominal abscess or peritonitis	1	3	0	0	1	2
Anastomotic leakage	1	3	4	15	5	9
Chylous fistula	4	13	2	8	6	11
Vocal cord palsy	2	6	0	0	2	4

pCR, pathological complete remission rate; TRG, tumor regression grade; ARDS, acute respiratory distress syndrome.

survival (progression or death) of all patients was 36.5 and 22.8 months, respectively (Figure 2). The event-free survival for patients with adenocarcinoma was 22.3 months, for patients with squamous cell carcinoma 27.9 months and for patients with a good response (TRG1 + 2) was 27.9 months compared with 17.0 months for poor responders (TRG > 2) (Figure 2).

Table 3 gives an overview of the sites of first failure and causes of death. Two patients died of unknown causes at home, one without and one with previously diagnosed relapse. Of the surgery-related deaths, only one patient had a known persisting tumor. Among the 27 patients who have died to date, tumor relapse was diagnosed in 21.

toxicity and treatment compliance

The toxicity profile of induction chemotherapy and chemoradiation is listed in Table 4. The hematologic and non-hematologic toxicity of induction chemotherapy was as expected and manageable. In seven patients, the dose of docetaxel, and in four patients the doses of both docetaxel and cisplatin, had to be reduced by 25% for the second cycle, mainly because of gastrointestinal toxicity.

Of 65 patients undergoing chemoradiation, 54 (83%) received full-dose radiation therapy together with all weekly doses of both drugs. Nine of the remaining 11 patients received full-dose radiation therapy but missed one weekly dose of chemotherapy. Of the two remaining patients, one patient stopped chemoradiation after 27 Gy because of unacceptable pain due to dysphagia. In the other patient, the first four weekly doses of chemotherapy were withheld because of covered esophageal perforation after induction chemotherapy. During chemoradiation, cisplatin had to be replaced by carboplatin in six patients due to impaired creatinine clearance and in one case because of grade 2 hearing loss. In four patients, feeding tubes were inserted before treatment; however, two of them were not needed because of rapid improvement of dysphagia during induction chemotherapy. Only two feeding tubes were inserted during neoadjuvant therapy because of poor nutritional status.

discussion

The objectives of this trial were to evaluate efficacy, toxicity, pattern of failure and feasibility of a taxane-containing,

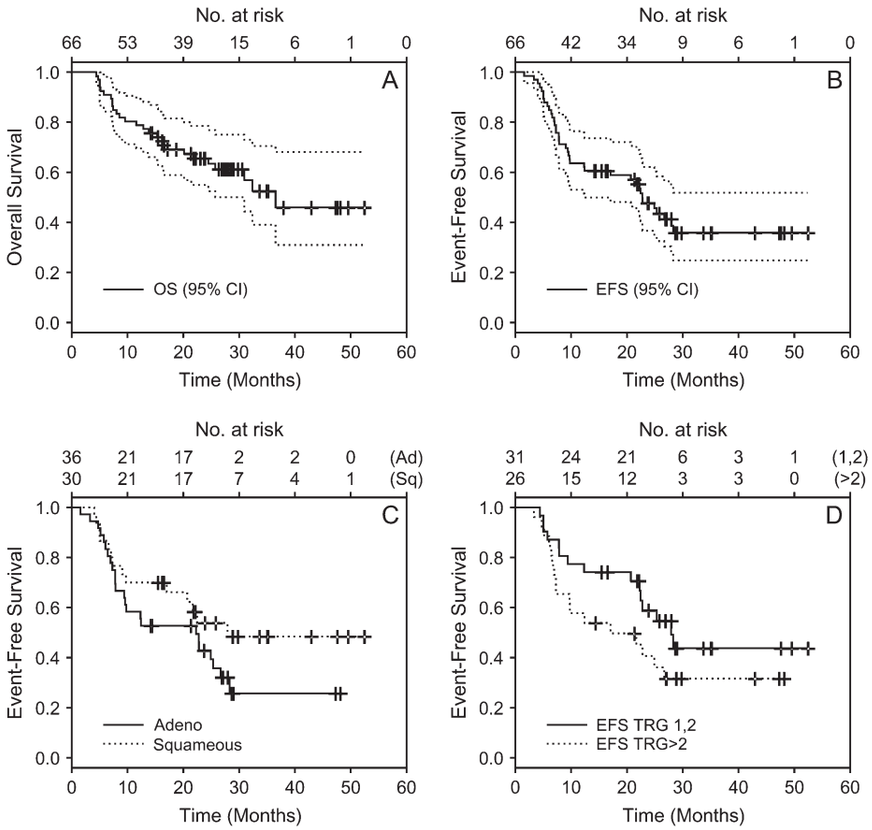

Figure 2. Kaplan–Meier plots according to intention-to-treat analysis showing (A) overall survival as time from registration to death; (B) event-free survival as time from registration to disease progression, relapse or death; (C) survival among patients according to histology type and (D) survival among patients according to histopathological response.

Table 3. Sites of first failure, survival status and causes of death

	Adenocarcinoma ($n = 36$)		Squamous cell carcinoma ($n = 30$)		Total ($n = 66$)	
	n	%	*n*	%	*n*	%
Alive and without residual or recurrent disease	12	33	15	50	27	41
Death without known recurrent disease	2	6	4	13	6	9
Relapse	22	61	11	37	33	50
Residual disease (R1/R2)	2	6	2	7	4	6
Locoregional recurrence	7	19	3	10	10	15
Distant metastases	12	33	2	7	14	21
Local recurrence and distant metastases	1	3	4	13	5	8
Deaths	17	47	10	33	27	41
Cancer related	13	36	6	20	19	29
Chemoradiation related	0	0	0	0	0	0
Surgery related	1	3	4	13	5	8
Death from other cause without tumor	1	3	0	0	1	2
Death from unknown cause	2	6	0	0	2	3

multimodal treatment strategy for patients with locally advanced esophageal carcinoma in a multicenter setting. Nearly all centers treating patients with esophageal cancer in Switzerland, a country of 7 million inhabitants, participated in this trial. Over 80% of patients included in the study had T3 tumors, most of them with node-positive disease, representing a poor-prognosis group of patients. However, patients with more extensive disease were excluded with good reliability because disease stage was accurately determined using CT scan, endosonography and, in most cases, a PET scan. The feasibility of this neoadjuvant regimen was very encouraging regarding the compliance with the study protocol in a multicenter setting and the adverse events. Sixty-three out of 65 nonprogressing patients received two cycles of induction chemotherapy,

Table 4. Adverse events of the preoperative regimen

Adverse events	Induction chemotherapy ($n = 66$)				Neoadjuvant chemoradiotherapy ($n = 65$)			
	All grades		Grade 3/4		All grades		Grade 3/4	
	n	%	*n*	%	*n*	%	*n*	%
Anemia	59	89	2	3	64	98	1	2
Thrombocytopenia	26	39	0	0	41	63	2	3
Neutropenia	44	67	34	52	9	14	0	0
Dysphagia	58	88	3	5	58	89	5	8
Mucositis	8	12	3	5	7	11	1	2
Diarrhea	25	38	7	11	5	8	0	0
Nausea	33	50	1	2	36	55	0	0
Vomiting	13	20	2	3	20	31	0	0
Febrile neutropenia	11	17	11	17	0	0.0	0	0
Neuromotor	1	2	0	0	2	3	0	0
Neurosensory	0	0	0	0	0	0	0	0
Hearing impairment	7	11	0	0	3	5	0	0
Alopecia	40	61	0	0	55	85	0	0
Asthenia	35	53	4	6	42	65	4	6
Dermatology	0	0	0	0	15	23	0	0
Other toxicity	58	88	6[a]	11	55	85	8[b]	12

[a]Dyspnea ($n = 1$), syncope ($n = 1$), colitis ($n = 1$), loss of appetite ($n = 1$), infection ($n = 1$) and dehydration ($n = 1$).
[b]Dyspnea ($n = 1$), pneumonia ($n = 1$), syncope ($n = 1$), dehydration ($n = 2$), hypokalemia ($n = 1$), arrhythmia ($n = 1$) and anorexia ($n = 1$).

full-dose radiation therapy and at least four of five weekly doses of concomitant chemotherapy. Of note, severe chemoradiation-related mucositis and dysphagia (grade 3 and 4) occurred in <10% of patients. The two cycles of induction chemotherapy contributed to improved swallowing and nutritional status in patients originally presenting with relevant tumor-related dysphagia. The low incidence of inserted feeding tubes during neoadjuvant therapy supports this observation. We speculate that the replacement of fluorouracil, frequently used in this situation, with docetaxel may have contributed to the decreased severity of mucositis as well.

Eighty-six percent of all included patients underwent surgery following induction chemotherapy and chemoradiation therapy. Ninety-three percent of all operated patients underwent an R0 resection, an important factor for long-term survival. The per-protocol definition of surgical mortality ending after 30 days, as in most other comparable trials, was low. However, the effective surgery-related mortality after neoadjuvant chemoradiation was 8.8% after taking into account later deaths that were clearly surgery related. This is similar to other trials of preoperative chemoradiation [2, 5, 15, 21], even including those reporting single-center experience [5, 21].

Postoperative complications included three cases of acute respiratory distress syndrome and eight cases of severe pneumonia, possibly related to the intensive type of chemoradiation. From our point of view, the centralization of care to experienced centers for this type of surgery remains crucial to reduce the complication rate further. Overall, the feasibility rate of this regimen was 82% on an intention-to-treat analysis, well within the feasibility target of this trial.

One primary efficacy end point of this trial was pCR rate. Ajani et al. [22] reported in 2007 that the pathological stage of the resected specimen after neoadjuvant chemoradiation is a determinant of patient survival rather than baseline clinical stage. We decided to classify the tumor regression grade according to Mandard et al. [18]. The high reliability of the TRG determination in our trial was confirmed by central review similar to another group [23]. With a pCR rate of 23% of all included patients we failed to reach the prospectively defined goal of this trial regarding efficacy. During the conduct of our study, the Siewert group validated the Mandard pathologically documented response classification and showed no significant survival difference between TRG1 (pCR) and TRG2 (1%–10% residual tumor cells) [24]. When using the Mandard histopathological classification, the line between no residual cancer cells (TRG1) and very rare residual cancer cells (TRG2) is often arbitrary, and pathologists usually classify response as TRG2 if they are uncertain if scattered tumor cells are alive or dead. Therefore, our rather low pCR rate is not easy to compare with those derived from studies using other classification systems. The potential clinical benefit may be better appreciated taking as well into account the rate of TRG 2.

Including this aspect, the neoadjuvant regimen under study was efficacious, with 47% of patients reaching a good histopathological response (TRG 1 + 2) in an intention-to-treat analysis. This result correlated with excellent survival outcomes for this poor-prognosis group of patients, with a median overall survival of 36.5 months and a median event-free survival of 23 months for all patients. Most published phase II trials and some phase III trials are single-center studies, and therefore it is difficult to compare them with our trial. However, the outcomes of this multicenter trial compare favorably with reported results from other multicenter trials [8, 10, 11, 25], although this trial was conducted in a community-based setting without high-volume centers. A reason for the favorable outcome could be the inclusion of a very homogeneous group of accurately staged patients. Other studies found a correlation

between histopathological response and survival [9, 24, 26], a finding that is supported by our results. However, in our study, patients with squamous cell cancer had a better response rate and survival than patients with adenocarcinoma, although not statistically significant. One could think that the adding of a taxane is more efficient for patients with squamous cell carcinoma than for patient with adenocarcinoma.

The prognosis of locally advanced esophageal cancer remains poor, and further investigations of neoadjuvant therapy should aim to improve efficacy while maintaining feasibility and acceptable toxicity. From our point of view, surgery so far remains an essential modality for achieving locoregional control of this disease as shown in several publications [15, 16, 27]. However, both the achievement of symptom relief with neoadjuvant therapy or, conversely, deterioration of overall condition may prevent patients from undergoing planned surgery in randomized trials. This may weaken the surgical arm and also be responsible for the lack of documented significant benefit of neoadjuvant strategies. This neoadjuvant regimen represents a suitable backbone for further investigation given its high efficacy with regard to R0 resection rate, response rate and event-free survival as well as high patient compliance and feasibility in a multicenter, community-based setting.

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